1.0 INTRODUCTION

Vical Inc. is currently conducting a multicenter Phase II trial of Allovectin-7 in patients with metastatic disease of five tumor types including melanoma, lymphoma, breast, renal cell and colorectal carcinoma. Allovectin-7 is a plasmid DNA agent encoding both the heavy and light chains of the MHC (major histocompatibility complex) class I antigen, HLA-B7 and β2 microglobulin, formulated with a cationic lipid. The agent is administered intralesionally. The rationale for the Phase II trial was developed from the preclinical and Phase I clinical observations that gene transfer, gene product expression and the triggering of a cell-mediated immune response could be safely and reproducibly accomplished. Clinical benefit was observed in several patients with advanced melanoma in the Phase I trials.

Allovectin-7's product concept is based on the observation that tumors often lose their ability to present antigens due to quantitative or qualitative deficiencies in MHC class I expression (1). Gene transfer of MHC class I HLA-B7 to tumor cells represents a form of "substitution therapy" to restore deficient antigen expression and trigger an antitumor immune response. HLA-B7 was chosen because it is a relatively infrequent haplotype and an allogeneic immune response would be triggered independently of tumor antigens in HLA-B7 negative patients.

In parallel with the U.S. Phase I clinical trials, Dr. Hulbert Silver at the British Columbia Cancer Agency evaluated the administration of Allovectin-7 in seven advanced melanoma patients without pre-selecting the HLA haplotype. Three of the seven patients treated were HLA-B7 positive. A significant tumor response was observed in three patients with two qualifying as partial clinical remissions. Two of the three responders were HLA-B7 positive (2). This observation raises the possibility that Allovectin-7 may be an active immunotherapeutic irrespective of the allogeneic immune activation. This corresponds with preclinical animal models that show an inverse relationship between tumor aggressivity and MHC class I expression (3). To further explore this possibility, Vical is conducting an additional Phase II protocol to determine the safety and efficacy of Allovectin-7 in HLA-B7 positive (and negative) melanoma patients. The study design is similar to the ongoing Phase II protocol with the dosing schedule adjusted to mirror the BCCA study regimen.

Vical Inc. is also providing Allovectin-7 for a squamous cell carcinoma head and neck cancer trial being conducted under an Investigator IND held by Jack L. Gluckman, M.D. at the University of Cincinnati Medical Center. The study design includes 4 intratumoral injections of Allovectin-7 using the same dosing regimen as in the multi-center Phase II Vical-sponsored clinical trial, VCL-1005-201. So far, 7 patients have been treated on this protocol. One of the patients has had a complete remission and a second patient experienced a marked reduction in tumor size after only one injection. Because of these promising responses, Vical proposes to expand this study to additional sites and sponsor the trial under the Vical IND,

2.0 BACKGROUND AND RATIONALE

2.1 Overview

Squamous cell carcinoma (SCCa) constitutes the vast majority of head and neck cancers. If identified early, these cancers can be treated relatively easily, either surgically or radiotherapeutically with an excellent cure rate. Unfortunately, most cancers are diagnosed relatively late with the cancer at an advanced stage. The standard form of treatment for these patients with advanced head and neck SCCa is surgical resection followed by radiation therapy, but with a five year survival of under 50%. In addition, there is a significant subset of patients who are so advanced at the time of presentation that they are regarded as incurable by conventional therapy, including chemotherapy, which has yielded little improvement in survival of these patients. Likewise, patients whose cancer recurs after conventional therapy have a dismal prognosis. Of equal concern, is the quality of life for these patients which can be extremely poor. Local disease often interferes with vital functions, e.g. swallowing, breathing, etc.(4).

Patients presenting at an advanced stage of disease or with recurrence would provide an ideal model to study using the gene therapy immunotherapeutic Allovectin-7. The cure rate with other therapies is extremely poor and the tumors are easily monitored. It is hoped that Allovectin-7 may cause sufficient local control that patient survival may be prolonged and morbidity decreased.